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Original article

Urinary Vitamin D Binding Protein as a Biomarker to Assess Steroid Responsiveness in Childhood Idiopathic Nephrotic Syndrome

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Abstract

Background: Nephrotic syndrome (NS) is the most common glomerular disease in children. It is characterized by recurrent attacks of proteinuria, hypoalbuminemia, and edema. The purpose of this study was to evaluate the value of urinary vitamin D binding protein (uVDBP) as a biomarker for differentiating steroid-resistant nephrotic syndrome (SRNS) from steroid-sensitive nephrotic syndrome (SSNS). **Methods:** This was a prospective case-control study conducted with 40 children aged 2-17 years diagnosed with idiopathic NS in the pediatric department of Benha University Hospital. The study period was from April 2022 to March 2023. The participants were divided into three groups: Group A included 20 children with SRNS, Group B included 20 children with SSNS, and Group C included 20 healthy children as a control group. **Results:** uVDBP levels were significantly different across the groups: 701.5 ng/mL (±153.1) in Group A, 483.6 ng/mL (±157.8) in Group B, and 423.9 ng/mL (±171.8) in Group C, with a highly significant difference ($p<0.001$). uVDBP showed a significant positive correlation with the urinary albumin creatinine ratio ($p<0.001$) and a significant negative correlation with serum albumin ($r=-0.411$, $p=0.001$). A ROC curve of uVDBP was conducted to discriminate between nephrotic syndrome groups. uVDBP showed moderate accuracy (AUC=0.833) for discrimination between nephrotic syndrome groups. **Conclusion:** uVDBP levels were significantly different among the three groups (SRNS, SSNS, and healthy controls). Our findings suggest that uVDBP could be a potential biomarker for distinguishing between SRNS and SSNS in pediatric patients with nephrotic syndrome.

Key words: Urinary Vitamin D Binding Protein, Steroid Responsiveness, Childhood, Idiopathic Nephrotic Syndrome**.**

Introduction

Nephrotic syndrome (NS) is a common glomerulopathy that occurs in children. The disorder is distinguished by episodic relapses involving edema, proteinuria, and hypoalbuminemia. The two prevalent forms of the disease often identified in histopathological studies of invasive renal biopsy, are minimal-change disease (MCD) and focal segmental glomerulosclerosis (FSGS) (1).

Children with steroid-resistant nephrotic syndrome (SRNS) are at higher risk of worsening conditions and developing complications compared to children with steroid-sensitive nephrotic syndrome (SSNS). Furthermore, reports indicated that the number of SRNS cases is escalating, likely due to the increasing number of cases diagnosed with FSGS worldwide. FSGS is the second leading cause of end-stage renal disease (ESRD) and chronic renal failure in childhood (2).

Responsiveness to steroid therapy has been reported to provide a better prediction of prognosis compared to a renal biopsy study. Hence, children with idiopathic nephrotic syndrome (INS) complete an imperative trial of high-dose steroid therapy (for a variable duration of up to three months), which can be considered as both therapeutic and diagnostic intervention. If successful remission is not attained, the patient is presumed to have SRNS and a biopsy study is warranted to identify the histopathological type (3). On the other hand, identifying SRNS (specifically FSGS) is commonly missed with a single kidney biopsy because of the focal nature of the glomerular lesions, necessitating multiple biopsies for accurate diagnosis of FSGS (4).

Vitamin D deficiency is a common complication in NS, primarily due to urinary losses of vitamin D binding protein (uVDBP). In children with NS, a greater decline in vitamin D levels has been observed in SRNS as compared to SSNS, suggesting that the severity of uVDBP loss is more pronounced in SRNS than in SSNS. In that regard, uVDBP levels were assessed in SRNS and SSNS patients from India and the United States (US) and significantly higher concentrations were reported in SRNS as compared to SSNS (5). However, SSNS subjects with proteinuria on urinalysis showed a higher trend of uVDBP levels than those in SSNS cases without proteinuria. This raised questions about whether increased levels of uVDBP reflect more pronounced proteinuria rather than the disparity in steroid responsiveness in INS patients. Additionally, when examining the SRNS groups separately, reported uVDBP levels in the studied populations from the US and India were far from equivalent. uVDBP levels in the SRNS groups from both studies (the American and the Indian, respectively) were 13659 (median; IQR 477–22,979) and 701.12 (mean; SD ± 371.64) ng/mL (6).

The aim of this study was to evaluate the value of uVDBP as a biomarker for differentiating steroid-resistant nephrotic syndrome from steroid-sensitive nephrotic syndrome.

Patients and methods

This is a prospective case-control study that assessed uVDBP levels in children with steroid-sensitive and steroid-resistant nephrotic syndrome. A total of 60 patients were involved in this study, including 20 children with SRNS, 20 children with SSNS, and 20 healthy children as a control group. Participants were recruited from the outpatient clinic and inpatient units at Benha University Hospital. The study was conducted over a one-year period, from April 2022 to March 2023.

An informed written consent was obtained from the patients' parents. Each patient's parent received an explanation of the study's purpose and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University **(MS 9-2-2021)**.

Inclusion criteria were children aged 2-17 years, diagnosed with idiopathic nephrotic syndrome (diagnostic criteria for NS include heavy proteinuria, hypoalbuminemia (serum albumin <2.5 g/dL) and serum cholesterol >200 mg/dL) (7), both sexes.

Exclusion criteria were congenital NS, NS secondary to systemic diseases such as systemic lupus or IgA nephropathy, patients with impaired kidney function tests, and history of gross hematuria

Grouping: The participants were divided into three groups: Group A: included 20 children with SRNS (SRNS is defined as a failure to respond to standard steroid treatment (2 mg/kg/day) for at least eight weeks) (8), Group B: included 20 children with SSNS (SSNS is defined as the ability to achieve remission within eight weeks after initial diagnosis in response to steroid treatment, evidenced by normalization of protein urine reading to a negative reading on a urine dipstick) (8), Group C: included 20 healthy children as a control group.

All studied cases were subjected to the following: Full history taking with a special focus on [demographics, clinical presentation, duration of symptoms, current remission/relapse status, and the history of response to steroids]. **Full clinical examination including** [anthropometric measurements (weight, height, BMI calculation), blood pressure assessment, evaluation of edema, ascites, cardiac involvement, dizziness, infections**]. Biochemical investigations** comprised complete blood count (CBC), kidney function tests [including urea, creatinine], cholesterol, serum albumin and urinary albumin /creatinine ratio and urine analysis by dipstick.

Blood sample collection: under completely sterile conditions, 5 ml of fresh venous blood were collected. One milliliter of this blood was placed into an

EDTA-containing vacutainer and mixed, for a CBC test. The remaining blood was collected in an empty tube for further analyses. The serum was separated for kidney function tests, serum albumin, and serum cholesterol measurements.

The levels of uVDBP were established utilizing enzyme-linked immunosorbent assay (ELISA) kits employed a double-antibody sandwich technique to detect uVDBP levels. Urine samples for patients were collected with the establishment of the diagnosis of childhood INS.

The urine samples were collected in sterile containers and centrifuged for 20 minutes at 3000 rpm. The uVDBP level was determined using a Human Vitamin D-binding protein (DBP) ELISA Kit (Catalogue No. 201-12-1403) in accordance with the manufacturer's guidelines. This was accomplished following appropriate chemical principles. Urine VDBP data were analyzed raw and also normalized to urine creatinine.

Sample size:

The sample size was calculated based on the study done by (9). With a sample size of 24 (12 per group), we had a power of 95% to assess whether urinary vitamin D binding protein is significantly higher in SRNS (mean value of 701±372) compared to SSNS (mean value of (253±66), using a 2-sample means test and a significance level of 0.05. In this study, we recruited 20 patients for each group and added an additional 20 participants serving as the healthy control group; hence, the total sample size was 60 participants. The sample size was calculated using the following formula:

$$n = 2\left[\frac{(z_{\alpha/2} + z_{\beta}) * \sigma}{\mu_1 - \mu_2}\right]^2$$

N: sample size, $Z_{\alpha/2}$ = 1.96 (the critical value that divides the central 95% of the Z distribution from the 5% in the tails), Z_{β} = 1.64 (the critical value that separate the lower 5% of the Z distribution from the upper 95%), σ = 372 (the estimate of the standard deviation of the SRNS), µ1 = 701 (mean value of urinary vitamin D binding protein in SRNS) µ2 = 253 (mean value of urinary vitamin D binding protein in SSNS), So, by calculation, the sample size will be 20 per group.

Statistical analysis:

Statistical analysis was done by SPSS v28 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by ANOVA (F) test with post hoc test (Tukey). Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analyzed by Kruskal-Wallis test with Mann Whitney-test to compare each group. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant. Pearson

correlation was done to estimate the degree of correlation between two quantitative variables. The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups. The optimum cut off point was defined as that which maximized the AUC value. AUC is that a test with an area greater than 0.9 has high accuracy, while 0.7–0.9 indicates moderate accuracy, 0.5–0.7, low accuracy and 0.5 a chance result.

Results

The data indicated no significant demographic differences among the three groups in terms of age and gender distribution. In terms of blood pressure, SBP and DBP measurements were significantly different between the studied Groups (p= 0.022 and <0.001 respectively). According to clinical presentation among studied groups, edema was significantly more common in Group A (100%) and Group B (95%) compared to Group C (10%), with a highly significant difference (p<0.001). Frothy urine was present in 70% of Group A and 45% of Group B, but only in 10% of Group C. This difference was statistically significant (p=0.044). GI manifestations (GIT upset and N/V) were not significantly different between the studied groups. Diarrhea was negative in all studied groups. **Table 1**

Regarding complete blood picture results, neutrophil percentages were significantly different among the groups, with mean values of 40% in Group A and 60% in both Groups B and C. This difference was highly significant (p<0.001). Lymphocyte percentages also showed significant differences, with mean values of 50% in Group A, 40% in Group B, and 30% in Group C (p<0.001). Other parameters didn't show significant differences between the studied groups. According to renal functions, blood urea levels and serum creatinine were not significantly different in the studied groups (p>0.05). Serum albumin levels showed significant differences: Group A had a mean of 3 mg/dL, Group B 3.2 mg/dL, and Group C 3.9 mg/dL. This variation was highly significant (p<0.001). Similarly, serum cholesterol levels differed significantly among the groups. The mean values were 338.2 mg/dL in Group A, 193.4 mg/dL in Group B, and 169 mg/dL in Group C (p=0.004). The mean albumin/creatinine ratios were significantly higher in Group A and B compared to Group C. These differences were statistically significant (p<0.001). **Table 2**

uVDBP levels were significantly different across the groups: 701.5 ng/mL (±153.1) in Group A, 483.6 ng/mL (±157.8) in Group B, and 423.9 ng/mL (±171.8) in Group C, with a highly significant difference (p<0.001). **Table 2**

uVDBP showed significant positive correlation with SBP (p=0.017), DBP (p=0.004) , serum cholesterol (p=0.020) and albumin creatinine ratio (p<0.001). uVDBP showed significant negative correlation with lymphocytes (p<0.001),

neutrophils (p<0.001) and serum albumin (r=-0.411, p=0.001). No significant correlations were found with BMI, hemoglobin, hematocrit, platelet count, total leucocytic count (TLC), urea and creatinine. **Table 3**

uVDBP showed moderate accuracy AUC (AUC=0.853), discrimination between Group A and control group. uVDBP showed moderate accuracy AUC (AUC=0.738), discrimination between Group B and control group. uVDBP showed moderate accuracy AUC (AUC=0.719), for discrimination between Nephrotic syndrome groups and control group. uVDBP showed moderate accuracy AUC (AUC=0.833), for discrimination between Nephrotic syndrome groups. Best cut off value and performance characteristics are shown in **Table 4; Figure 1**

Table 1. Demographic data, Blood pressure and Clinical presentation among the studied groups

		Group A	Group B	Group C	Test	p
		n=20	n=20	n=20		
Age (years)	**Mean±SD**	8.08 ± 4.41	6.92 ± 3.00	6.67 ± 3.32	t=0.864	0.427
Gender	**Male**	13(65%)	15(75%)	11(55%)	X2=0.615	0.735
	Female	7(35%)	5(25%)	9(45%)	X2=1.143	0.565
SBP	**Mean±SD**	114.5±12.1	107.4±9.5	104.8±8	7.597	0.022*
DBP	**Mean±SD**	76.5±8.6	69.5±6.7	68.3±5.2	13.931	<0.001*
Edema	**Negative**	0(0%)	1(5%)	18(90%)	X2=14.976	0.001*
	Positive	20(100%)	19(95%)	2(10%)	X2=32.316	<0.001*
Frothy urine	**Negative**	6(30%)	11(55%)	18(90%)	X2=8.72	0.013*
	Positive	14(70%)	9(45%)	2(10%)	X2=6.229	0.044*
GIT upset	**Negative**	7(35%)	15(75%)	18(90%)	X2=9.700	0.008*
	Positive	13(65%)	5(25%)	2(10%)	X2=4.850	0.088
N/V	**Negative**	19(95%)	20(100%)	19(95%)	X2=0.034	0.983
	Positive	1(5%)	0(0%)	1(5%)	X2=1.000	0.607
Diarrhea	**Negative**	20(100%)	20(100%)	20(100%)	X2=0.000	1.000

SBP: systolic blood pressure, DBP: diastolic blood pressure, GIT: gastrointestinal tract, N/V: Nausea and vomiting. * for significant p value (<0.05)

Table 2: Laboratory investigations and Urinary Vitamin D Binding Protein among studied groups

		Group A	Group B	Group C	Test	p
		n=20	n=20	n=20		
TLC (/µL)	**Mean± SD**	12.3±3.4	10.7±2.4	11±4.1	3.041	0.219
Neutrophils (%)	**Mean± SD**	40±10	60±10	60±20	16.474	<0.001*
Lymphocytes (%)	**Mean± SD**	50±10	40±10	30±10	18.361	<0.001*
Hemoglobin (g/dL)	**Mean± SD**	12.5±1.2	12.2±0.8	11.7±1.6	4.184	0.123
Hematocrit	**Mean± SD**	37.2±3.2	36.8±2.7	35.5±5.2	2.482	0.289
Platelet (/µL)	**Mean± SD**	412.7±114.1	373.3±182.8	336.7±104.5	4.732	0.094
Urea (mg/dL)	**Mean± SD**	23±8	20.1±5.9	26.1±9	4.784	0.091
Creatinine (mg/dL)	**Mean± SD**	0.6±0.2	0.6±0.1	0.6±0.1	0.288	0.866
Serum albumin (mg/dL)	**Mean± SD**	3±0.7	3.2±0.6	3.9±0.5	19.042	<0.001*
Serum cholesterol (mg/dL)	**Mean± SD**	338.2±236.2	193.4±96.1	169±65.3	11.0877	0.004*
Urinary Albumin /creatinine ratio	**Mean± SD**	62905.8 ±232798.1	3034.3 ± 4896	27.1±1.5	42.703	<0.001*
uVDBP (ng/mL)	**Mean± SD**	701.5±153.1	483.6±157.8	423.9±171.8	21.603	<0.001*

TLC: Total leucocytic count, * for significant p value (<0.05)

Table 3: Correlation between Urinary Vitamin D Binding Protein and other studied parameters

Variable	r_s	p
BMI	-0.011	0.934
SBP	0.308	0.017*
DBP	0.365	0.004*
Hemoglobin	0.079	0.550
Hematocrit	0.007	0.957
Platelet	0.179	0.171
TLC	0.227	0.081
Lymphocyte	0.442	<0.001*
Neutrophil	-0.425	<0.001*
Urea	-0.025	0.853
Creatinine	-0.121	0.359
S. albumin	-0.411	0.001*
S. cholesterol	0.300	0.020*
Alb/Cr ratio	0.520	<0.001*

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TLC: Total leucocytic count, r_s: Spearman correlation, * for significant p value (<0.05)

Table 4: Validity of uVDBP for discrimination between Group A & control group, Group B and control group, Nephrotic syndrome groups and control group, and between Nephrotic syndrome groups

	AUC	95% CI	p	Cut off	Sensitivity (%)	Specificity (%)
Group A & control	0.853	0.705 to 0.944	<0.001*	485.02	95	65
Group B & control	0.738	0.575 to 0.864	0.01*	435.54	90	80
Nephrotic syndrome & control	0.719	0.588 to 0.827	0.002*	485.02	75	65
Nephrotic syndrome groups	0.833	0.681 to 0.932	<0.001*	501.92	100	55

AUC: area under ROC curve , CI: confidence interval, * Significant ≤0.05

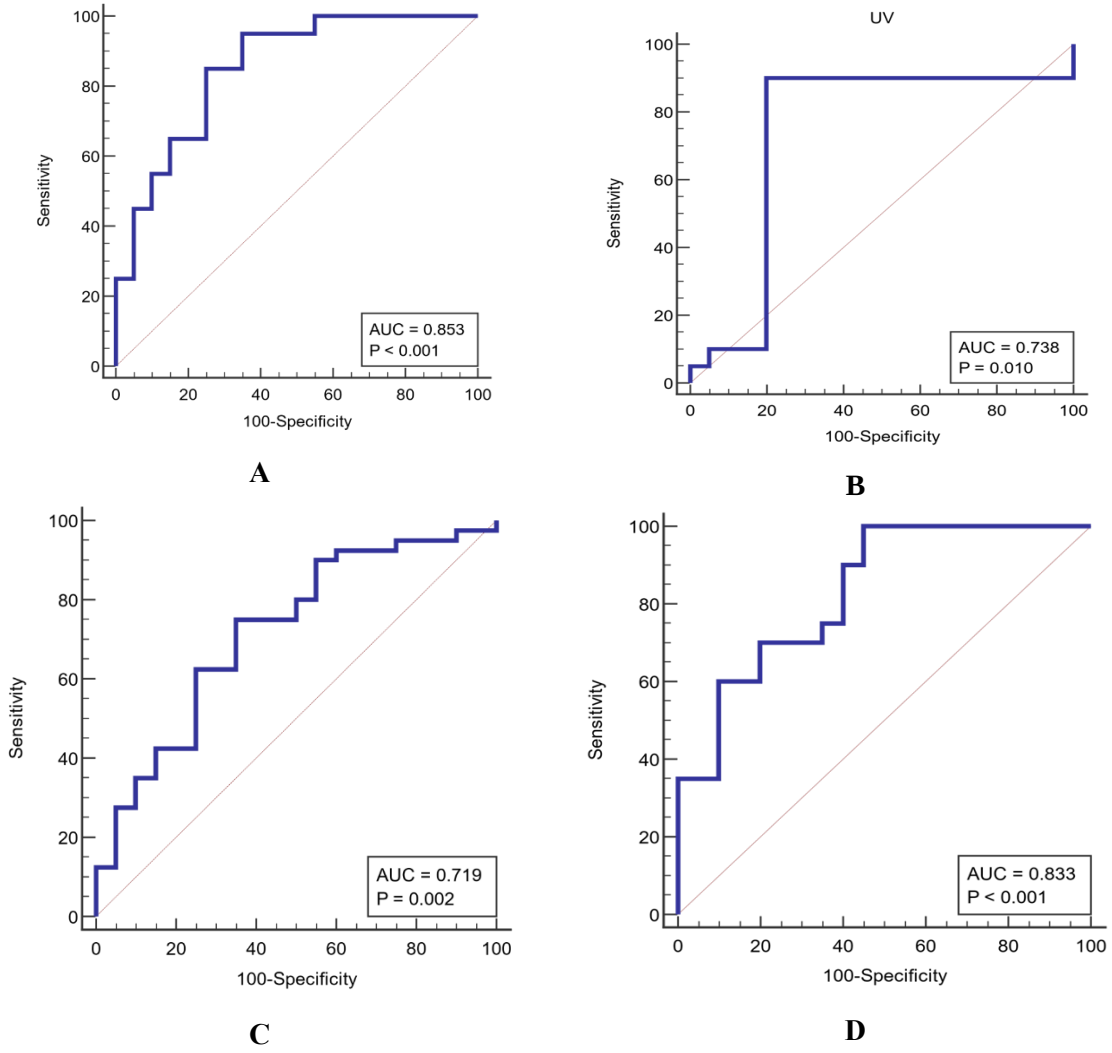

Figure 1: A) ROC curve of uVDBP for discrimination between Group A and control group, B) between Group B and control group C) between nephrotic syndrome groups and control group, D) between Nephrotic syndrome groups

Discussion

In our study, according to differences in demographic data between the studied groups, the mean ages (in years) were 8.08 ± 4.41, 6.92 ± 3.00, and 6.67 ± 3.32 for Groups A, B, and C, respectively. Overall, the data indicated no significant demographic differences among the three groups in terms of age. This is in agreement with (8) study in which mean age for his study group was 7.1 years ± 4.3.

In our study, in terms of blood pressure, SBP and DBP measurements were significantly different between the studied Groups (p= 0.022 and <0.001 respectively). In contrast**,** (9) showed no significant difference was found between patients & control group regarding blood pressure.

In our study, according to renal functions, blood urea levels and serum creatinine were not significantly different in the studied groups (p>0.05). Our study agrees with (10)**,** who reported that no differences were detected, (serum creatinine and blood urea), between INS groups and controls.

This is in agreement with (11)**,** who found that there is no statistically significant difference between patient group (children with idiopathic nephrotic syndrome) and control group as regards blood urea and serum creatinine.

In our study, according to levels of uVDBP among the studied groups, uVDBP levels were significantly different across the groups: 701.5 ng/mL (±153.1) in Group A, 483.6 ng/mL (±157.8) in Group B, and 423.9 ng/mL (±171.8) in Group C, with a highly significant difference (p<0.001).

In harmony, (12) revealed that uVDBP absolute levels at the time of diagnosis were significantly higher in patients with NS compared to healthy controls (P < 0.001). Also, those with relapsing NS had significantly higher uVDBP absolute levels compared to those experiencing the first attack of NS (P = 0.014).

In accordance, (13) Investigated the association between uVDBP levels and steroid responsiveness in children with idiopathic NS and found that uVDBP levels were significantly higher in patients with SRNS than in patients with SSNS (701.12 ± 371.64 vs. 252.87 ± 66.34 ng/mL, P < 0.001). This also agrees with (14), who showed that uVDBP concentrations are markedly increased in patients with SRNS versus patients with SSNS and healthy controls (*P* < 0.001). These results remained significant after correcting for urine creatinine.

In our study, uVDBP showed significant positive correlation with urinary albumin creatinine ratio (p<0.001). A previous study by (15) investigated VDBP in NS children and showed strong correlations between uVDBP and proteinuria. In addition, (14) reported positive correlation between uVDBP excretion and proteinuria (r = 0.66, P < 0.001).

In our study, ROC curve of uVDBP was conducted for discrimination between Nephrotic syndrome groups. uVDBP showed moderate accuracy AUC (AUC=0.833), for discrimination between Nephrotic syndrome groups. A previous study by (16) reported that, the ROC curve analysis of uVDBP found a significantly reliable discriminatory power to discern patients with SRNS from patients with SSNS (AUC= 0.909, $p < 0.0001$).

This result was consistent with the results from similar studies in the United States and India (AUC= 0.87 and 0.897, respectively; $p < 0.0001$) (13, 14). (13) reported ROC curve analysis to evaluate the ability of different urinary markers to predict steroid responsiveness in children with idiopathic NS. According to their results, uVDBP showed an area under the curve (AUC) of 0.897 indicating that uVDBP had a significant predicting power with cutoff value of 303.8ng/mL. They concluded that uVDBP can be used to predict the steroid responsiveness accurately in NS children.

Conclusion:

Our study showed that uVDBP levels were significantly different among the three groups (SRNS, SSNS, and healthy controls). Additionally, uVDBP demonstrated a significant positive correlation with urinary albumin creatinine ratio and a significant negative correlation with serum albumin. Our findings suggest that uVDBP could be a potential biomarker for distinguishing between SRNS and SSNS in pediatric patients with nephrotic syndrome.

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